

## REMARKS

Upon entry of the present amendments, claims 14-39 are pending.

Claims 14, 21, 27, and 34 are amended herein. The foregoing amendment is made without any intention to abandon the subject matter of the claims as filed September 17, 2003, but the intention that claims of the same, lesser or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. Applicant believes that the present amendment does not add new matter.

Support for the claim amendments can be found in the claims and the specification, as follows:

The preamble of claims 14, 21, 27, and 34 are amended herein to clarify the claims. Support for these amendments can be found in, e.g., Specification page 36, line 20 through page 37, line 3; page 38, line 4 through page 39, line 9; and page 44, line 5 through page 46, line 2. No new matter has been introduced by the present amendments.

### 35 U.S.C. §112, 2<sup>nd</sup> paragraph

Claims 14-39 are rejected under 35 U.S.C. §112, 2<sup>nd</sup> paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that “[i]t is unclear as to what applicant intends to convey by ‘amphipathic antioxidants’ in claim 14 (also claims 21 and 27). See, August 5, 2005 Office Action at pages 2-3. Applicant traverse.

The Specification clearly defines what the term ‘amphipathic antioxidants’ in the claims intends to convey. For example, at page 19, lines 8-25, the Specification provides:

Non-enzymatic antioxidants may be classified as either hydrophilic or hydrophobic. Alpha tocopherol and beta carotene are classified as hydrophobic, whereas ascorbic acid is hydrophilic. Glutathione shares characteristics of being both hydrophilic and hydrophobic. The characteristics of being either attracted to water (hydrophilic) or being repelled by water (hydrophobic) will determine the orientation of the particular antioxidant within the cytosol and/or membrane of the cell or liposome. Therefore free radical reactions occurring in the cytosol would be quenched by either glutathione or ascorbic acid, free radicals occurring within the membrane would be quenched by alpha-tocopherol and/or beta-carotene. Each of the non-enzymatic antioxidants react more favorably with certain free radicals as opposed to others. For example, singlet oxygen reacts with beta carotene; tocopherol is known to react with alkyl free radicals; glutathione and ascorbic acid are likely to be unselective in their reaction with various free radicals occurring within the cytosol.

Moreover, FIG. 8 illustrates the distribution and relationship of various antioxidants within the lipid and aqueous phases of the liposome and the Specification provides numerous

examples of amphipathic antioxidant compositions (see, e.g., Specification page 7, line 6 through page 9, line 7 and Examples at pages 49-60). Accordingly, Applicant submits that the term ‘amphipathic antioxidants’ in the claims is clearly defined in the Specification and request reconsideration and withdrawal of this rejection.

### 35 U.S.C. §103

Claims 14-23 and 27-36 are rejected under 35 U.S.C. §103(a) as being unpatentable over Halliwell (1991) Free Radicals in Biology and Medicine (hereinafter “**Halliwell**”) or Packer (1992) Proc. Soc. Exper. Biol. Med (hereinafter “**Packer**”) in view of U.S. Patent 5,013,556 (hereinafter “**Woodle**”), EP 0455 386 (hereinafter “EP ‘386”), and JP 62178521 (hereinafter “JP ‘521”). Applicants traverse.

Claims 14-23 and 27-36 are drawn to either a method of treating an injury in a mammal induced by exposure to a caustic gas or a method for reducing the deleterious effects of a caustic gas. The claims require the administration of an amphipathic antioxidant composition. The composition requires: (i) a population of liposomes suitable for undergoing peroxidation and lysis; and (ii) at least two non-enzymatic amphipathic antioxidants. Furthermore, the claims require that the amphipathic antioxidant composition reduces the tissue damage induced by the caustic gas.

None of **Halliwell**, **Packer**, **Woodle**, EP ‘386, or JP ‘521, either alone or in combination, bear on the patentability of claims 14-23 and 27-36.

#### **Halliwell and Packer**

The Examiner states that **Halliwell** and **Packer** “show the involvement of free radicals in various diseases and the counter acting effects of various antioxidants against the free radicals.” The Examiner admits that these two references fail to teach the administration of antioxidants in liposomes or the administration of the combination of antioxidants in the treatment of free radical induced disease conditions. August 5, 2005 Office Action at page 4. However, **Halliwell** and **Packer** are fatally deficient in teaching or even suggesting several other aspects of the present invention, as claimed herein. First, although these references may suggest the use of antioxidants in various diseases, there is no teaching or suggestions of using an antioxidant composition for treating an acute injury induced by a caustic gas. Further, these references not only fail to disclose the combination of antioxidants, these references fail to

disclose, teach or suggest the **amphipathic antioxidant composition** of the present invention. As required by the present claims, the amphipathic antioxidant composition of the present invention requires: (i) a population of liposomes suitable for undergoing peroxidation and lysis; and (ii) at least two non-enzymatic, amphipathic antioxidants. These required claim elements are simply lacking in both **Halliwell** and **Packer**.

***Halliwell and Packer in view of Woodle, EP '386, and/or JP '521 in further view of UNIMED***

None of **Woodle**, **EP '386**, **JP '521**, or **UNIMED** either alone or in combination, help cure the deficiencies of **Halliwell** and **Packer** (if these combinations were proper, which they are not). The reasoning for this position was clearly set out in the Amendment and Response filed May 18, 2005 and are maintained in the present Amendment and Response.

The Examiner states that Applicant's arguments that there is no teaching in any of the cited prior art for using antioxidants for treating an injury induced by a caustic gas was not found to be persuasive "since the references clearly teach the damage caused by **free radicals** and the ability of the antioxidants to protect the host against the damage caused by the free radicals." The Examiner alleges that "it is within the skill of the art to recognize that the antioxidants would react with the free radicals in the same way irrespective of the source of the free radicals." August 5, 2005 Office Action at page 6.

Applicant strongly disagrees with the Examiner's assertions. **Halliwell** and **Packer** may suggest the ability of antioxidants to protect the host against the damage caused by the free radicals, but there is no empirical demonstration that antioxidants can be used to treat diseases or injuries induced by free radicals *in vivo*. Accordingly, **Halliwell** and **Packer** do not provide a reasonable expectation of success.

None of **Woodle**, **EP '386**, **JP '521**, or **UNIMED** help cure this deficiency of **Halliwell** and **Packer**.

**Woodle** is directed to increasing the circulating time of a liposome encapsulated drug and demonstrating the sustained release of liposome encapsulated drugs. There is not one word in **Woodle** regarding the use of antioxidants or liposome encapsulated antioxidants for treating an injury induced by exposure to a caustic gas.

**EP '386** relates to fat-based food products, and particularly to a problem encountered in fat systems in cream-filled biscuits in which an additive formulated as an emulsion contains

water droplets that migrate to the biscuit and adversely affect eating quality. A skilled artisan would not be motivated by the teachings of this reference to use the fat-based medium with liposomes containing vitamin C and vitamin E disclosed in **EP '386** to treat an injury induced by exposure to a caustic gas, as claimed in the present invention.

**JP '521** is directed to the prevention of oxidation of hemoglobin and an artificial erythrocyte using an aqueous solution of hemoglobin containing vitamin C in a liposome and a membrane containing vitamin E. Like **Halliwell and Packer**, **JP '521** also fails to provide any evidence that liposomal compositions of antioxidants can be used to treat an injury induced by exposure to a caustic gas, as claimed in the present invention.

Finally, **UNIMED** does not cure the deficiencies of **Halliwell and Packer**. As stated in the description of ONDROX™ provided under the section entitled: "What exactly is ONDROX™?":

**ONDROX™ is not a drug, nor is it a treatment for any disease.** ONDROX™ is a nutritional supplement... [Emphasis added.]

A person skilled in the art would not administer a "nutritional supplement" which is clearly labeled as a nutritional supplement and not a drug to a mammal exposed to a caustic gas and nor would the skilled artisan expect that **UNIMED** would produce a reduction of the deleterious effects of in a mammal exposed to a caustic gas.

None of the six references cited by the Examiner provides a shred of evidence, let alone a reasonable expectation of successfully using antioxidants for the treatment of an injury induced in a mammal by exposure to a caustic gas, as claimed in the present invention.

In contrast, the present application teaches that liposomes containing amphipathic antioxidants can be used to treat injuries induced by exposure to a caustic gas. See, e.g., Specification page 36, line 20 through page 37, line 3; page 38, line 4 through page 39, line 9. Moreover, empirical evidence was made of record in the parent application, USSN 07/989,593 (now US Patent No. 6,764,693), which clearly demonstrates that the amphipathic antioxidant liposomes of the present invention can be used to reduce the damage induced by exposure to a caustic gas. Both of the Declarations of Dr. Milton Smith (dated November 1, 2001 and May 19, 2003) provide *in vivo* data showing the ability of several different liposomal amphipathic antioxidant compositions were effective in reducing the acute lung injury induced by the mono-functional analog of mustard gas, half-mustard gas (HMG, 2-chloroethyl ethyl sulfide). See,

e.g., paragraphs 4-8 of the May 19, 2003 Declaration of Dr. Smith. Indeed, liposomes with two antioxidants were more effective than liposomes with only one antioxidant. See, e.g., paragraph 8 and Exhibit A of the May 19, 2003 Declaration of Dr. Smith. These data indicate that the antioxidant compositions of the above-referenced application are effective in reducing the acute lung injury induced by a caustic gas.

Accordingly, Applicant submits that the present claimed invention is not obvious in light of the six cited references and request reconsideration and withdrawal of the rejection.

### CONCLUSION

On the basis of the foregoing amendments, applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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